## REMARKS

The office action of August 8, 2011 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is requested. Claim 1 has been amended by this response. No new matter has been added. More specifically, claim 1 has been amended to correct antecedent basis.

### Rejection under 35 U.S.C. §112

Claim 1 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner states that "[a]lthough the specification on page 30 asserts that Thioredoxin (TRX) has inhibitory effect with respect to protease such as cysteine protease and metalloprotease, Farina et al. (2001) and Sahlin et al. (2000) at least partially contradict" (present office action dated August 8, 2011, page 3, lines 9-12) and then explains why he believes these two references teach away from the instant invention.

The Examiner appears to be considering solely the teachings of two references to then conclude that undue experimentation would be required to practice the claimed invention. References that teach away from an invention do not even fall squarely into any of the *In re Wands* factors. If they needed to be categorized in some way, they may be part of the state of the prior art and/or the level of predictability of the art. But, when considering the state of the prior art with respect to enablement, the question is whether the prior art has the experimental tools necessary to practice the claimed invention without undue experimentation, not whether the prior art teaches away from the claimed invention. Similarly, the level of predictability of the art considers the experimental tools necessary to practice the claimed invention. In addition, these are only two factors, and the Examiner can not ignore what is taught in the application when concluding that the claim is not enabled.

Regarding Farina, Farina observed MMPP-9 activity by gelathinolytic metalloproteinase activity (Gelathinase assay) (page 406, right column, second paragraph) and quantified MMP-9 activity by densitometer (page 406, left column, last paragraph, through right column, first paragraph). That is to say, MMP-9 activity was assessed <u>indirectly</u> by gelathinolytic

metalloproteinase activity, and the quantification of MMP-9 activity was determined by densitometer of the Western blot bands. The method used in Farina cannot show precise quantification because MMP-9 activity is not directly determined.

Sahlin suggests that thioredoxin and glutaredoxin may have downstream effects including a possible role as general disulfide reductants in tissue remodeling. Sahlin then states that inactivation of tissue inhibitors (TIMP-1 and TIMP-2) of metalloproteineases (MMP) by disulphide reduction may promote MMP-2 and MMP-9 activity involved in collagen breakdown (page 1151, right column, lines 13-19).That data was not shown.

The present application includes a working example. This is very strong evidence that undue experimentation would not be required in order to practice the invention. More specifically, Example 1, starting on page 30 of the application states:

"Example 1

Test on protease-inhibiting effect of TRX in a test tube

Inhibiting effect of TRX for caspase-1, MMP-1, MMP-9 was tested.

Assay method:

Caspase-1

A test according to Thornberry NA (Nature 356(30):768-775, 1992) was carried out. Specifically, recombinant human caspase-1 was allowed to react with 20 μM Ac-YVAD-AMC at 37 ℃ for 3 hours. After that, the fluorescent level of AMC (7-amino-4-methylcoumarin) was determined twice (the determination was carried out by MDS Pharma Services Japan (Kyoto, Japan))

MMP-1,9

Recombinant MMP-1 (peptide laboratory (Kyoto, Japan)), recombinant MMP-9 (peptide laboratory (Kyoto, Japan)) were allowed to react with 50 μM P3163-v (MOCAc-Pro-

Leu-Gly + Leu-Azpr(DNP)-Ala-Arg-NH2) (peptide laboratory (Kyoto, Japan)) at 37 ℃ for 2 hours before the fluorescent level of AMC (7-amino-4-methylcoumarin) was determined twice.

Results

Under the presence of 100 μg/mL purified TRX, caspase-1 was suppressed by 21 %. Also, MMP-1 and MMP-9 were suppressed respectively by 47 % and by 76 % under the presence of 100 μg/mL purified TRX.

This shows that TRX has an inhibitory effect with respect to protease such as cystein protease and metalloprotease."

This example uses a well known test (Thornberry NA) to determine that MMP-1 and MMP-9 are inhibited by TRX. When searching for "Thornberry N.A. et al., Nature 356 (30): 768-774, 1992" through PubMed, the Applicant found over two hundred pieces of literature citing this reference (attached please find Thornberry N.A. et al., Nature 356 (30): 768-774, 1992 as Exhibit A.).Clearly, the Thornberry NA test is well known by those of ordinary skill in the art, and is used routinely by those skilled in the art.

The Thornberry method is a method to identify whether a substance (hereinafter referred to as "A") has an inhibitory effect on a protease (hereinafter referred to as "B"), is well known by those skilled in the art, and is explained further here. A substance that is specifically destroyed by B is hereinafter referred to as "C". The fluorescence-labeled C is reacted with B in test tubes i) in the absence of A (test tube (i)) and ii) in the presence of A (test tube (ii)), for 2 hours at 37 degrees Celsius. Then, the fluorescence from test tubes (i) and (ii) is measured. A's inhibitory rate is determined from the difference between test tube (i) and test tube (ii). For example, in test tube (i), the rate of C which is destroyed by B is P% (theoretically, B destroys 100% of C (maximum)). In test tube (ii), B destroys C by Q%. A's inhibitory rate is P% - Q%. This method is a routine method, well known by those of ordinary skill in the art.

In Example 1 of the present application, MMP-1 or MMP-9 are the proteases "B". The fluorescence-labeled P3163-v (MOCAc-Pro-Leu-Gly + Leu-Azpr(DNP)-Ala-Arg-NH2) was reacted with MMP-1 or MMP-9 i) in the absence of TRX (test tube (i)), and ii) in the presence of TRX (test tube (ii)) for 2 hours at 37 degree Celsius. Then, the fluorescence from test tube (i) and

test tube (ii) were measured, and TRX's inhibitory rate of MMP-1 or MMP-9 was determined from the difference between the fluorescence of test tube (i) and test tube (ii).

The example clearly shows that MMP-1 and MMP-9 were suppressed respectively by 47% and by 76% under the presence of 100μg/ml purified TRX, which has an active site of -Cys-X1-X2-Cys, where X1 and X2 are amino acid residues. Therefore, the example shows a protease inhibitor that satisfies all of the elements of claim 1. Therefore, undue experimentation would not be necessary.

Example 1 shows that thiroedoxin (TRX) has an inhibitory effect with respect to protease of caspase-1, MMP-1 and MMP-9. Therefore, one of ordinary skill in the art could use these results to suppress MMP-1 and/or MMP-9 proteases.

The animal models described in the present application are well known by those of ordinary skill in the art and are often used by those of ordinary skill in the art, as described in Shapiro, S.D. Animal Models for COPD, Chest, 117: 223S-227S, 2000, attached as Exhibit B). These animal models could be used by those skilled in the art to identify redox activity proteins having an active site of –Cys-X1-X2-Cys-, where X1 and X2 are amino acid residues, that inhibit MMP-1 and MMP-9 proteases, without undue experimentation.

Applicant believes that these amendments have fully addressed the Examiner's rejections, and the claims are now in condition for allowance. Reconsideration and withdrawal of the rejection are respectfully requested.

**Conclusion**

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicants' attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

"Recognizing that Internet communications are not secured, I hereby authorize the PTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file."

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Dated: February 6, 2012